REMARKS

Applicants thank the examiner for indication that the objection to the drawing has been withdrawn. Applicants also thank the examiner for the withdrawal of several of the § 112 rejections and the § 102 and § 103 rejections. In addition, applicants thank the examiner for withdrawing two of the provisional obviousness-type double patenting rejections.

After entry of the above amendments, claims 1, 3-10, 12-13, 15-21, 25-29, 31-38, 40, 42-44 and 46-63 are pending. Claims 30, 41 and 45 have been cancelled. Claims 1, 6, 13, 20, 29, 38, 40, 42-44 and 46-49 have been amended to more clearly define the present invention. Applicants respectfully submit that no new matter has been added by the above amendments. In addition, new claims 56-63 have been added. Applicants submit that these claims are fully supported by the specification.

Objection to the Arrangement of the Specification

Applicants submit that entry of the above amendments to the specification obviate the objection to the Arrangement of the Specification and request that it be withdrawn.

Section 112, First Paragraph, Rejections

Claims 1, 3-10, 12, 13, 15-21, 25-35, 38, 40-44 and 46-55 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled because it is unclear what exactly is meant by the term "hetero." Claims 1, 3-10, 12, 13, 15-21, 25-35, 38, 40-44 and 46-55 also stand rejected under § 112, first paragraph, as not enabled because the phrase "functional group" is unduly functional and the examples of carbonyl and hydroxy are too diverse. Applicants respectfully submit that the amendments to claims 1, 13, 20 and 29 wherein the phrase "or one or more carbonyl groups or one or more ether or thioether groups" has been added and the phrase "and optionally containing one or more hetero atoms which may form part of, or

be, a functional group" has been deleted, obviate these two rejections. Therefore, applicants request that the rejections be withdrawn.

Claims 31 and 42 stand rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the invention at the time the application was filed because R_7 is not described as an electron donating group in the specification and because "treating a condition which can be treated by regulation of gene expression" is not described in the specification. Applicants respectfully submit that there is support for the amendment to claim 31 on page 11 at line 1, where it is stated that "R_7 is preferably an electron donating group." The quoted phrase appears in claim 38 not in claim 42. However, applicants have amended claim 38 to remove this phrase. Applicants, therefore, respectfully request that this rejection be withdrawn.

Claims 38, 40, 41 and 43-45 stand rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The examiner asserts that the above-listed claims are directed to various methods of treatment with substituted pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one compounds. The examiner also asserts that the specification provides no definitive evidence to correlate any one disorder selected from those disclosed in the specification with the disclosed compounds. Moreover, the examiner asserts that there is no "silver bullet" for treating cancer generally. Applicants respectfully submit that the amendments to claims 38, 40, 43 and 44 and the cancellation of claims 41 and 45 obviate this rejection. Applicants direct the examiner to Examples 5, 6a, 6b, 6c, 7, 8, 9 and 10 on pages 198-214 of the specification for support for these amendments. Applicants therefore request that the rejection be withdrawn.

Claims 46-49 stand rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants submit that these claims are enabled by the disclosure of the specification. Specifically, applicants direct the examiner to page 12, lines 3 to page 13, line 3 of the specification. Applicants submit that one of ordinary skill in the art would be able to make and/or use the claimed compositions. Therefore, applicants request that the rejection be withdrawn.

Section 112, Second Paragraph, Rejections

Claims 4, 5, and 42 stand rejected under § 112, second paragraph, as being indefinite because the use of the variable R in the definition of R is indefinite. Applicants submit that the amendments to the claims obviate these rejections and respectfully request that the rejection be withdrawn.

Claims 30 and 42 stand rejected under § 112, second paragraph, because the definition of R'_8 and R''_8 where R'_8 and R''_8 are a nitrogen protecting group is broader in scope than that which is defined in R. Applicants respectfully submit that the cancellation of claim 30 obviates this rejection and request that it be withdrawn.

Claim 42 also stands rejected under § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully submit that the amendments to claim 42 delineating the steps of the claimed method obviate the rejection and request that it be withdrawn.

Claims 1, 3, 6-10, 12, 35-38, 40-44 and 46 stand rejected under § 112, second paragraph, as vague and indefinite in that it is not known what is meant by the proviso where when A is a single bond, then R_2 is not $CH=CR^AR^B$, where R^A and R^B are independently selected from COR^C, $CONH_2$, $CONHR^C$, $CONR^C_2$, cyano or phosphonate. The examiner asserts that at no time is R_2 $CH=CR^AR^B$, where R^A and R^B are independently selected from

COR^C, $CONH_2$, $CONHR^C$, $CONR^C{}_2$, cyano or phosphonate. Applicants respectfully submit that the amendment to claim 1 obviates this rejection and request that it be withdrawn.

Claim 6 stands rejected under § 112, second paragraph, as vague and indefinite in that it is not known what is meant by the definition of R_2 where R_2 forms part of a conjugated system with a double bond of a pyrrolobenzodiazepine. Applicants submit that the amendments to claim 6 obviate the rejection. Applicants further direct the examiner to page 1 of the specification where the A-, B- and C-rings of pyrrolobenzodiazepenes are labelled. Applicants respectfully request that this rejection be withdrawn.

Claims 7, 8, 9 and 10 stand rejected under § 112, second paragraph, because there is insufficient antecedent basis for the limitation "unless the compound is a dimer." Applicants respectfully submit that this rejection is obviated by the amendment to claim 1 removing the limitation to dimers. Applicants, therefore, respectfully request that this rejection be withdrawn.

Claims 13, 15-19, 35-38, 40-44 and 47 stand rejected under § 112, second paragraph, as vague and indefinite in that it is not known what is meant by the definition of R'_2 where R'_2 is selected from: O. Applicants respectfully submit that the amendments to claim 13 obviate this rejection and request that it be withdrawn.

Claims 31 and 42 stand rejected under § 112, second paragraph, as vague and indefinite in that it is not known what is meant by electron donating group. Applicants respectfully direct the examiner to page 11, lines 1-6, of the specification where "electron donating group" is defined as "a moiety covalently attached to a compound which is capable of increasing electron density in other parts of the compound." (Page 11, lines 4-6.) Applicants, therefore, request that this rejection be withdrawn.

Claims 38, 40, 41, 43 and 44 stand rejected under § 112, second paragraph, as vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does

not set forth any steps in determining which diseases are capable of being mediated by regulation of gene expression. Applicants respectfully submit that the amendments to these claims obviate this rejection. Therefore, applicants respectfully request that this rejection be withdrawn.

Claim 45 stands rejected under § 112, second paragraph, as lacking antecedent basis for the limitation "methylidene." Applicants respectfully submit that the cancellation of claim 45 obviates the rejection and request that the rejection be withdrawn.

Claim Rejections Under § 101

Claim 42 stands rejected under 35 U.S.C. § 101 because the claimed recitation of a use without setting forth any steps involved in the process results in an improper definition of a process. Applicants submit that the amendments to claim 42 delineating the steps of the claimed method obviate the rejection and respectfully request that it be withdrawn.

Claim Rejections Under § 102

Gregson et al.

Claims 50-55 stand rejected under 35 U.S.C. § 102(a) as anticipated by Gregson et al. (Chem. Commun.). The examiner cites Gregson et al. as teaching the compounds, compositions and method of use of the compounds of formula **II** where R_6 is hydrogen, R_7 is methoxy, R_8 forms the dimer through the bridge $-O-(CH_2)_3-O-$, R_9 is hydrogen and R'_2 is CH_2.

As stated in the response filed August 22, 2002, Gregson et al. was published on May 7, 1999. Applicants respectfully direct the examiner's attention to the priority documents filed with the international application. Because applicants' priority date is August 27, 1998, Gregson et al. is not § 102(a) prior art, which requires the reference to be publicly known. Therefore, applicants respectfully request that this rejection be withdrawn.

Suggs et al.

Claims 20, 38, 40-44 and 48 stand rejected under § 102(a) as being anticipated by Suggs et al. (Tet. Lett.). The examiner cites Suggs et al. as teaching the compounds, compositions and method of use of the compounds of formula **III** where R_6 is hydrogen, R_7 is amino and R_8 and R_9 are hydrogen. Applicants respectfully submit that this rejection is obviated by the amendment to claim 20 limiting R_8 to amino. Therefore, applicants respectfully request that this rejection be withdrawn.

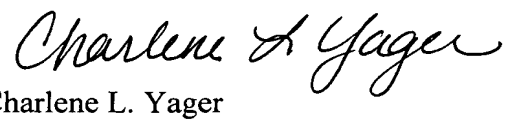
Provisional Obviousness-Type Double Patenting Rejection

Applicants maintain their position that the provisional obviousness-type double patenting rejection over Application No. 09/763,813 is improper for the reasons of record.

CONCLUSION

In view of the foregoing, applicants respectfully submit that the claims, as amended, are in condition for allowance. Applicants earnestly solicit a Notice of Allowance.

Respectfully submitted,



Charlene L. Yager
Reg. No. 48,887

Docket No.: 065435-9002
Michael Best & Friedrich LLP
One South Pinckney Street
P. O. Box 1806
Madison, WI 53701-1806
(608) 257-3501

Version With Markings

In the specification:

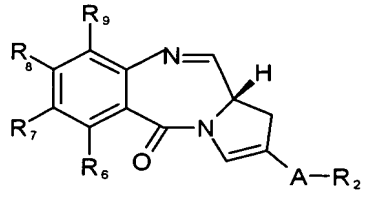
Please replace the paragraph at page 1, line 1 with the following:

-- [COMPOUNDS] PYRROLOBENZODIAZEPINES --

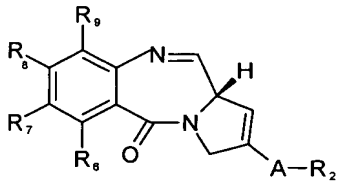
In the claims:

Please amend claim 1 as follows:

1. (Twice amended.) A pyrrolobenzodiazepine compound of the formula **Ia** or **Ib**:



(Ia)



(Ib)

wherein:

A is CH_2, or a single bond;

R_2 is selected from: R, OH, OR, CO_2H, CO_2R, COH, COR, SO_2R, CN, CH_2OR or $CH=CR^AR^B$, where R^A and R^B are independently selected from H, R^C, COR^C, $CONH_2$ $CONHR^C$, $CONR^C_2$, cyano or phosphonate, where R^C is an unsubstituted alkyl group having 1 to 4 carbon atoms;

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or one or more carbonyl groups or one or more ether or thioether groups, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, [and optionally containing one or more hetero atoms which may form part of, or be, a functional group];

and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above or where the compound is a dimer with each monomer being the same or

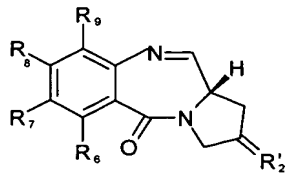
different and being of formula **Ia** or **Ib**, where the R_8 groups of the monomers form together a bridge having the formula -X-R^1-X- linking the monomers, where R^1 is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N; or R_7 and R_8 together form a group -O-$(CH_2)_p$-O-, where p is 1 or 2; with the proviso that when A is a single bond, then R_2 is not $CH=CR^AR^B$, where R^A and R^B are independently selected from H, R^C, COR^C, $CONH_2$, $CONHR^C$, $CONR^C{}_2$, cyano or phosphonate, where R^C is an unsubstituted alkyl group having 1 to 4 carbon atoms.

Please amend claim 6 as follows:

6. (Twice amended.) A compound according to claim 1, wherein A is a single bond, and R_2 is an aryl group, or an alkyl or alkaryl group which contains at least one double bond which forms part of a conjugated system with a double bond of [a] <u>the</u> pyrrolobenzodiazepine <u>compound C-ring</u>.

Please amend claim 13 as follows:

13. (Twice amended.) A compound of formula **II**:



(II)

wherein:

R'_2 is [selected from:] O;

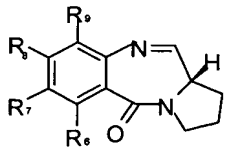
R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or one or more carbonyl groups or one or more ether or thioether groups, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, [and optionally containing one or more hetero atoms which may from part of, or be, a functional group];

and where the compound is a dimer with each monomer being the same or different and being of formula **II**, where the R_8 groups of the monomers form together a bridge having the formula -X-R^1-X- linking the monomers, where R^1 is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N.

Please amend claim 20 as follows:

20. (Twice amended.) A compound of the formula **III**:



(III)

wherein:

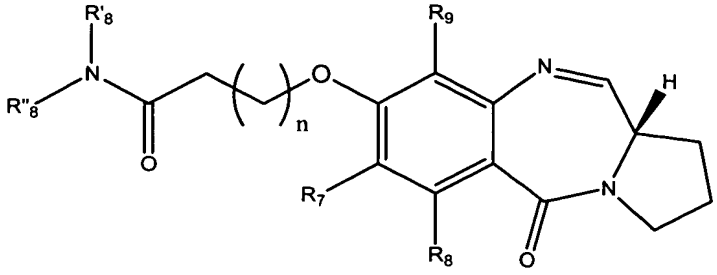
R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or one or more carbonyl groups, or one or more ether or thioether groups, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups[, and optionally containing one or more hetero atoms which may from part of, or be, a functional group];

and R_8 is [selected from H, R, OH, OR, halo,] amino[, NHR, nitro, Me_3Sn, where R is as defined above or the compound is a dimer with each monomer being the same or different and being of formula **III**, where the R_8 groups of the monomers form together a bridge having the formula -X-R^1-X- linking the monomers, where R^1 is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N; or R_7 and R_8 together form a group -O-$(CH_2)_p$-O-, where p is 1 or 2; wherein at least one of R_6, R_7, R_8 and R_9 is NH_2].

Please amend claim 29 as follows:

29. (Once amended.) A compound of formula **IV**:



(IV)

wherein:

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or one or more carbonyl groups, or one or more ether or thioether groups, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups[, and optionally containing one or more hetero atoms which may form part of, or be, a functional group];

R_8' and R_8'' are either independently selected from H, R or together form a cyclic amine; and

n is from 1 to 7.

Please amend claim 38 as follows:

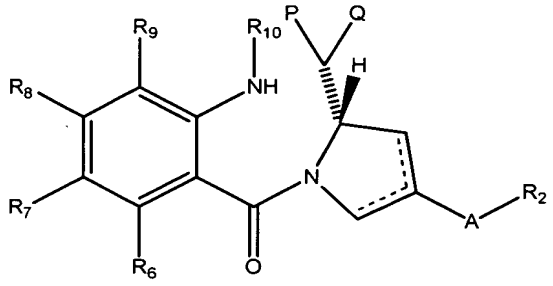
38. (Twice amended.) A method of treating cancer [a condition which can be treated by regulation of gene expression] comprising administering an effective amount of a compound according to claim 1, claim 13, claim 20 or claim [29] 50 to a patient in need of such treatment wherein the cancer is selected from lung cancer, colon cancer, CNS cancer, melanoma, renal cancer, breast cancer and ovarian cancer.

Please amend claim 40 as follows:

40. (Twice amended.) A method of treating cancer [a gene-based disease] comprising administering an effective amount of a compound according to [claim 1, claim 13, claim 20 or] claim 29 to a patient in need of such treatment wherein the cancer is selected from lung cancer, colon cancer, CNS cancer, melanoma, renal cancer and ovarian cancer.

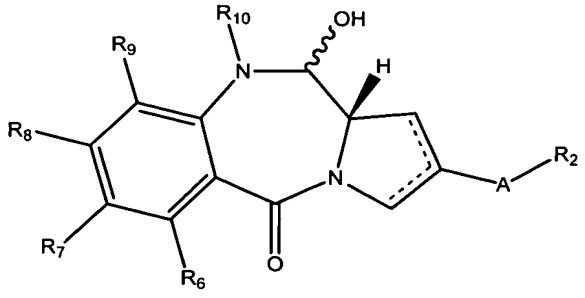
Please amend claim 42 as follows:

42. (Once amended.) A process for preparing a compound according to [any one of] claim[s] 1 [to 37] comprising cyclizing a compound of formula



wherein A, R_2, R_6, R_7, R_8 and R_9 are as defined in claim 1, R_{10} is a nitrogen protecting group and CPQ is a masked aldehyde;

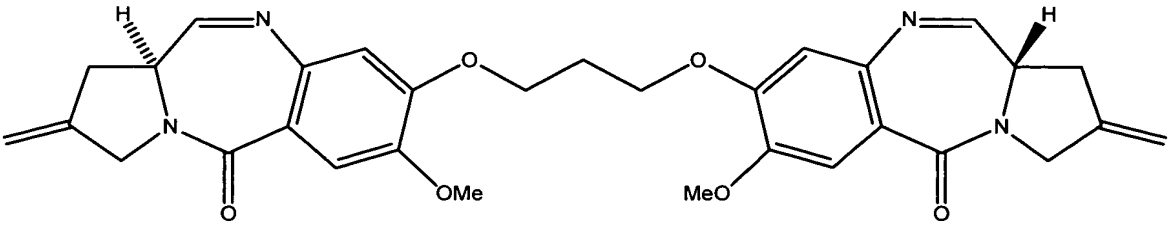
to a compound of formula



wherein A, R_2, R_6, R_7, R_8, R_9 and R_{10} are as defined above and converting the above compound to a compound according to claim 1.

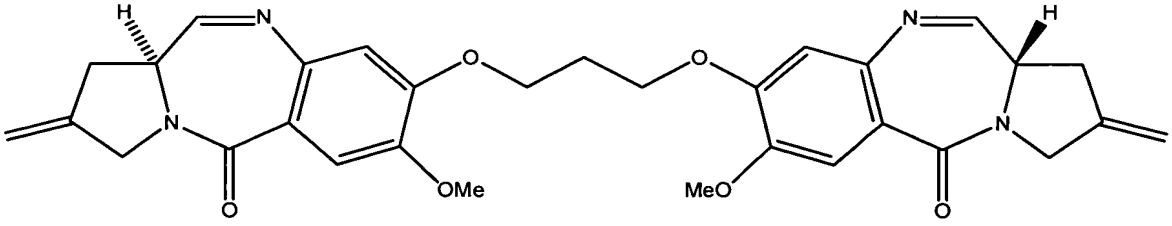
Please amend claim 43 as follows:

43. (Twice amended.) A method of treating a cisplatin-refractory disease comprising administering an effective amount [of a compound according to claim 1, claim 13, claim 20 or claim 29] to a patient in need of such treatment <u>of a compound of formula</u>



Please amend claim 44 as follows:

44. (Twice amended.) A method of inhibiting the growth of cisplatin-refractory cells which method comprises treating said cells with a compound [according to claim 1, claim 13, claim 20 or claim 29] <u>of formula</u>



Please amend claim 46 as follows:

46. (Once amended.) A [pharmaceutical] composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.

Please amend claim 47 as follows:

47. (Once amended.) A [pharmaceutical] composition comprising a compound according to claim 13 and a pharmaceutically acceptable carrier or diluent.

Please amend claim 48 as follows:

48. (Once amended.) A [pharmaceutical] composition comprising a compound according to claim 20 and a pharmaceutically acceptable carrier or diluent.

Please amend claim 49 as follows:

49. (Once amended.) A [pharmaceutical] composition comprising a compound according to claim 29 and a pharmaceutically acceptable carrier or diluent.